American Journal of Hematology 54:164–165 (1997)

Hb S/Hb Lepore With Mild Sickling Symptoms: A Hemoglobin Variant With Mostly δ-Chain Sequences Ameliorates Sickle-Cell Disease

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Three cases are reported of Hb S/Hb Lepore combination with very mild sickling manifestations. The presence of a nonα-chain variant with a high proportion of δ chain sequences, including 22 ala, appears to ameliorate sickle-cell disease. Efforts to increase the proportion of Hb A_2 may be beneficial in sickle-cell disease. Am. J. Hematol. 54:164–165

Key words: sickle-cell disease; Hb Lepore; Hb S; delta chain; Hb A_2

INTRODUCTION

Attempts to treat sickle-cell disease by increasing the proportion of Hb A_2 may have deleterious effects, including exacerbation of anemia [1]. However, constructs with the β-globin substitution 22-glu→ala inhibit Hb S polymerization [1]; Hb A_2 has 22 ala in the δ chain. Hb G-Coushatta is β22 glu→ala. Hb Lepore-Boston has mostly δ chain sequences, including 22 ala. It would be informative to examine sickle-cell disease severity in patients with the combination Hb S/G-Coushatta or Hb S/Lepore-Boston, since such experiments of nature might answer questions posed by recent reports [1,2].

We have not encountered a case of Hb S/Hb G-Coushatta, nor are we aware of any reported cases. In such a case, the proportion of Hb S should approximate that in Hb S trait, and not cause serious sickling. However, the Hb S/Hb Lepore combination may have enough Hb S to cause serious sickling, particularly if an excess of δ chains were to have harmful consequences, as has been asserted. Few such cases have been previously reported [3–5]. In 4 of 7 previously reported cases of HbS/Hb Lepore, sickling manifestations were mild. In 3 other cases, manifestations were severe, although Hb concentration in these cases ranged from 8–9 g/dl. Three of 4 cases with mild sickling features were age 57, 60, and 76 years.

We describe 3 cases of Hb S/Hb Lepore, with relatively mild manifestations.

Case 1 is a 23-year-old African-American male who has been repeatedly admitted to hospital for treatment of pain in his back or legs, but with no other manifestations of sickle-cell disease. Physical examinations have been unremarkable.

Case 2, the 26-year-old sister of case 1, has recurrent arthralgias and acute decline in Hb concentration associated with acute infections, but has rarely been transfused.

Case 3 is a 16-year-old Jamaican black male who has experienced a few episodes of knee or elbow pain. He has no other manifestations of sickle-cell disease. His physical examination was unremarkable.

In the specimens from cases 1 and 2, identification of Hb Lepore was made on the basis of its characteristic electrophoretic mobility and by isoelectric focusing and HPLC with a weak cationic exchange resin column. In the specimen from case 3, Hb Lepore was not suspected initially because of its high proportion. An abnormal glo-

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Received for publication 23 May 1996; Accepted 18 June 1996.

TABLE I. Laboratory Data

Case no.	Hb conc. (g/dl)	RBC × 10^{12}/l	MCV (fl)	Hemoglobin components (%)[a]				
				A	F	A_2	S	Lepore
1	9.9	3.93	77.8	0	8	2	77	12
2	10.4	4.13	74.6	0	7	4	78	11
3	11.9	5.61	66.5	0	5	3	72	20

[a]Proportions of Hb components have been rounded to nearest whole integer.

bin chain, not β^S, was separated by HPLC, and its tryptic peptides were examined. Peptides 10 and 11 had δ sequences; peptide 12 had a β sequence; these results were consistent with Hb Lepore-Boston.

The microcytosis in these cases was due to Hb Lepore trait. The mildness of the symptoms suggests that the presence of a Hb variant with δ-chain sequences has no adverse effect when present together with high proportions of Hb S, but rather ameliorates sickle-cell disease. The high proportion of Hb Lepore in case 2 supports this conclusion.

Nagel et al. [1] indicate that human δ-globin chains bind avidly to mouse red-cell membranes, causing severe erythrocyte deformity and hemolysis. Their observations, in conflict with the mildness of the HbS/Hb Lepore sickling disorder, may be explained thus: either 1) human δ-globin chains may not have the same deleterious effect on human erythrocyte membranes, or else 2) the short segment of the human δ-globin chain, beyond the point at which crossing-over occurs in Hb Lepore-Boston, may confer the deleterious effects observed by Nagel et al. [1], but the long segment containing δ-chain sequences, from amino-acid residue 1–87, does not.

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